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Short communication

Radioligand-binding study of noribogaine, a likely metabolite of ibogaine

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Abstract

Radioligand-binding studies were performed to ascertain the actions of noribogaine, a suspected metabolite of ibogaine, on opioid receptors. Consistent with previous results, ibogaine showed highest affinity for κ opioid receptors ($K_i = 3.77 \pm 0.81 \mu\text{M}$), less affinity for μ receptors ($K_i = 11.04 \pm 0.66 \mu\text{M}$) and no affinity for δ receptors ($K_i > 100 \mu\text{M}$). Noribogaine showed a higher affinity than ibogaine for all of the opioid receptors: κ $K_i = 0.96 \pm 0.08 \mu\text{M}$, μ $K_i = 2.66 \pm 0.62 \mu\text{M}$ and δ $K_i = 24.72 \pm 2.26 \mu\text{M}$. These data suggest that noribogaine is active in vivo and that it may contribute to ibogaine's pharmacological effects.

Keywords: Ibogaine; Noribogaine; Desmethyl ibogaine; Opioid receptor

Ibogaine is a naturally occurring indole alkaloid currently under investigation as an agent to treat drug addiction. In rats, ibogaine has been shown to significantly decrease morphine [8] and cocaine [2] self-administration and to prevent morphine-induced release of extracellular dopamine in several brain regions [10]. Additionally, ibogaine has been shown to significantly inhibit morphine-induced locomotor activity in rats [12] and cocaine-induced locomotor activity in mice [14] and to affect the actions of amphetamine and cocaine on the mesolimbic dopamine system [1,11].

Little is known about the mechanism of action of ibogaine. However, because of its enduring anti-addictive properties and its short half life [6], it is suspected to produce lasting effects through a long-acting active metabolite. Ibogaine researchers suspect this metabolite to be noribogaine (desmethyl ibogaine, see Fig. 1) [3] which could be formed by *N*-demethylation of ibogaine. This manuscript details the receptor-binding properties of noribogaine with regard to known binding properties of ibogaine. Previously published binding data indicate that ibogaine has highest affinity for the κ opiate receptor ($K_i = 2.08 \mu\text{M}$) [4,13] and no affinity ($K_i > 100 \mu\text{M}$) for the δ or μ opiate receptors

[4]. The present study seeks to examine the binding affinities of noribogaine to determine if this potential ibogaine metabolite also binds to opioid receptors.

Radioligand-binding assays were performed in triplicate for competition studies in 2 ml volume containing 50 mM TRIS buffer, 10^{-5} naloxone (non-specific binding), radioligand, ibogaine or noribogaine and 1 ml tissue homogenate. The κ assay was performed using 1 nM [^3H]U69593 and calf cortex incubated for 30 min

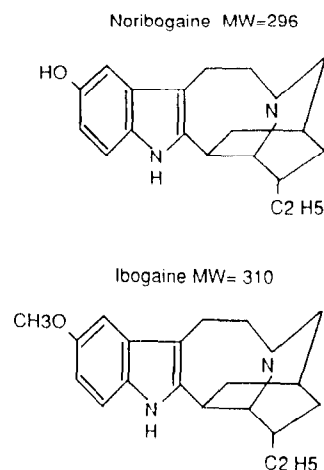


Fig. 1. Structures of ibogaine and its potential metabolite noribogaine.

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Table 1

Affinities of ibogaine and noribogaine for opiate receptors. Data are mean $\pm$ S.E.M. values of triplicate determinations from three experiments using different membrane preparations

Compound	K_i (μ M) $\pm$ S.E.M. κ (3 H-U69593)	K_i (μ M) $\pm$ S.E.M. μ (3 H-DAGO)	K_i (μ M) $\pm$ S.E.M. δ (3 H-DPDPE)
Ibogaine	3.77 $\pm$ 0.81	11.04 $\pm$ 0.66	> 100
Noribogaine	0.96 $\pm$ 0.08	2.66 $\pm$ 0.62	24.72 $\pm$ 2.26

at 37°C. The δ assay was performed using 1 nM [3 H]DPDPE and calf caudate incubated for 4 h at 25°C. The μ assay was performed using [3 H]DAGO and calf cortex and was incubated for 30 min at 37°C. After incubation, tubes were filtered through Whatman GF/B glass fiber filters with 10 ml cold 50 mM Tris-HCl buffer. The filters were counted by liquid scintillation spectrometry. Compounds were considered inactive at the defined opiate receptor if there was no inhibition at 100 μ M. Results were analysed using EBDA and RS1 (BBN).

Ibogaine K_i values from this experiment agree with previously published κ [4,13] and δ opioid data [4]. Previously, this laboratory has reported, using [3 H]carfentanil, a K_i of > 100 μ M for ibogaine at the μ receptor; although the reason is obscure, we have consistently found that ibogaine does have affinity for the μ receptor when [3 H]DAGO is used but not when [3 H]carfentanil is used as the radioligand. We, therefore, report in this study, contrary to previous results [4], that ibogaine does have affinity for the μ opioid receptor (K_i = 11.04 $\pm$ 0.66 μ M). Noribogaine is more active than ibogaine at both μ and κ opioid receptors and, unlike ibogaine, is active at the δ receptor. Complete binding results are summarized in Table 1 and

competition curves for ibogaine and noribogaine at the κ opioid receptor are illustrated in Fig. 2.

The increased affinity of noribogaine at the κ opioid receptor may be of significance. κ agonists have been shown to decrease morphine- and methamphetamine-induced locomotor activity in mice [9]. κ agonists have also been shown, like ibogaine, to decrease dopamine metabolite levels in the striatum [9,5] and to decrease dopamine release in the nucleus accumbens [7]. Thus, an ibogaine metabolite, such as noribogaine, which has a higher affinity for the κ receptor than does ibogaine itself, may be capable of producing greater effects than ibogaine. Consequently, noribogaine might have anti-addictive actions at lower (and, therefore, possibly less side-effect producing) doses than ibogaine. Clearly, more studies are necessary to ascertain noribogaine's potential use as a pharmacotherapy for drug addiction.

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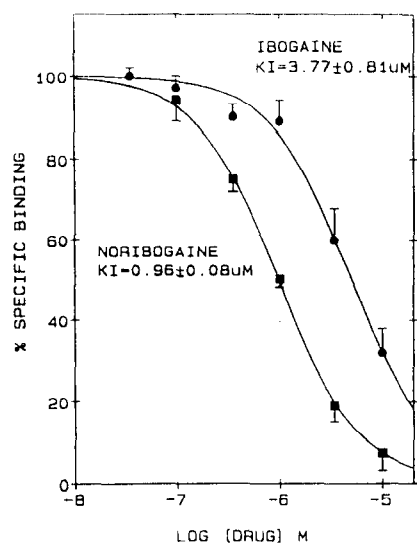


Fig. 2. Competition of ibogaine and noribogaine with 1 nM [3 H]U69593 for κ opioid receptor. Each data point represents triplicate determinations of three separate experiments using different membrane preparations.

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